Quick guide

Natural killer cells

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What are they? Natural killer (NK) cells are large, granular lymphocytes found mainly in peripheral blood, where they make up about 10% of the lymphocyte population. They are a first line of defense in the innate immune system and may also have a role in the adaptive immune system.

Why the provocative name? Well, it's easier to remember than 'CD3-negative, CD56 and/or CD16-positive lymphocytes'.

They first came to prominence… in the 1970s, because of their ability to spontaneously kill certain tumour cells.

What do they do? NK cells are equipped with cytotoxic granules that contain the arsenal of cytotoxic molecules used in killing virally infected and cancerous cells. They recognize their targets, in part, by means of activating signals that are only just beginning to be identified, but also by detecting cells that are deficient in cell-surface class I molecules of the major histocompatibility complex (class I MHC molecules). Tumour cells and cells infected with viruses have often lost their cell-surface MHC molecules, which makes them susceptible to attack. Healthy cells displaying self-MHC molecules are protected against attack by NK cells (see Figure).

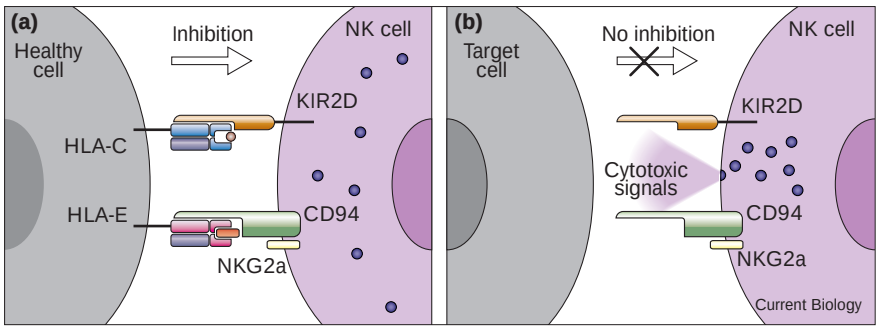
How do they work? When an NK cell is triggered to kill a target cell, cytotoxic granules are released. The granule contents can induce either osmotic lysis (necrosis) or suicide (apoptosis) of the target cell.

So, what's known about the receptors on NK cells? Human NK cells have two distinct types of surface receptor that recognize class I MHC molecules: members of the immunoglobulin superfamily (killer cell Ig-like receptors, or KIR), and the C-type lectin receptors, composed of a heterodimer of CD94 and an NKG2 protein. They interact with MHC class I molecules in different ways and each type of receptor has both inhibitory and activating forms. Inhibition dominates when both forms are expressed in a single cell. Diversity is a key feature of the KIR receptors. Unfortunately, this diversity also extends to the nomenclature, which makes reading the literature hard work. For example, the names p58.1, nkat-1 and 2DL1 all refer to one KIR receptor.

How do NK cell receptors cope with the diversity of MHC class I molecules? In humans, KIR receptors bind directly to the conserved sections of individual class I MHC molecules, whereas the CD94–NKG2a receptor recognises classical class I MHC molecules indirectly, using an adaptor molecule, the non-classical class I MHC molecule HLA-E. HLA-E binds the signal peptide of some, but not all, MHC molecules. On binding, HLA-E translocates to the cell surface, where it interacts with its inhibitory CD94–NKG2a receptor (see Figure).

What else do they do? Granule-mediated cytotoxicity is not their only weapon; NK cells also secrete tumor necrosis factor α and and can express the apoptosis FasL signal. In addition, they produce a range of cytokines, which allows them to regulate and participate in such immune processes as hemopoeisis, antibody production and early interferon γ production in infection.

Could we live without them? Perhaps, but probably not a long or healthy life. There is only one documented human case of an absolute NK cell deficiency, which was associated with recurrent life-threatening bacterial and viral infections.



(a) A healthy cell expresses class I MHC molecules at its surface (represented here by the human MHC molecules HLA-C and HLA-E). These interact with receptors (represented here by human KIR2D and CD94–NKG2a) on the NK cell surface and transmit an inhibitory signal to the NK cell, thus sparing the healthy cell from lysis. The signal peptide (red) of classical MHC class I allows HLA-E expression on the cell surface. (b) In a target cell (a virally infected or cancerous cell) class I MHC may be no longer expressed at the surface. This cell therefore does not inhibit NK cells and is killed. (Activating signals are less well understood and are not shown.)

Where can I find out more?

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